REMARKS

Claims 1, 3-4, 9-10, 12-15, 26, 28, and 43-48 constitute the pending claims in the present application. Applicants have canceled, without prejudice, claims 27 and 29 as well as withdrawn claims 16-25 and 30-42.

Claims 1, 3-4, 9-10, 12-15, 26, 28 have been amended. Claims 43-48 have been added. These new claims either depend from claim 1 or are closely related to claim 1, and thus belong to Group I. Applicants submit that no new matter has been introduced by the claim amendments or the new claims. The amended claims are fully supported by the specification (e.g., pages 43-44, Example 3) and original claims (e.g., claims 20-22). Support for new claims 43-48 can be found, for example, on page 26, lines 2-8. Applicants further submit that the amendments and cancellations are made merely to expedite allowance of claims directed to most commercially relevant embodiments of the present invention. Applicants reserve the right to pursue claims of similar or differing scope in the future.

Applicants note with appreciation that the Preliminary Amendment filed on January 3, 2004 has been entered in full.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Election/Restriction

The Examiner has acknowledged Applicants' election, with traverse, of Group I (claims 1, 3-4, 9-10, 12-15, and 26-29) in the Response filed on May 3, 2004.

Priority

The Examiner asserts that priority has not been granted for Provisional Application No. 60/189,739 under 35 U.S.C. 119(e) because the provisional application does not provide support for the limitation recited in claim 1. Applicants reserve the right to claim the priority under 35 U.S.C. 119(e) upon indication of allowable subject matter in the future.

Objection to the specification

Specifically, the Examiner objects to the specification because the designation for the sequence identifier is improper. Applicants have amended the specification as suggested by the Examiner.

The Examiner further objects to the specification at the "Brief Description of the Drawings." Applicants have amended the "Brief Description of the Drawings" section in the specification to obviate the objection.

Claim rejections under 35 U.S.C. §112, first paragraph

Claim 15 is rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to enable one of skill in the art to practice the claimed invention. Applicants traverse these rejections to the extent that they are maintained in light of the amended claims.

The Examiner acknowledges that the specification is enabling for a method for attenuating expression of a target gene in a cell, wherein said expression of the target gene is attenuated by up to 7.4 fold. However, the Examiner asserts that the specification does not reasonably provide enablement for a method for attenuating expression of a target gene in a cell, wherein said expression of the target gene is attenuated by at least 10 fold.

Solely to expedite prosecution of the application, Applicants have amended claim 15 to clarify that "expression of the target gene is attenuated by at least 5 fold." The amendments are not made in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope.

Applicants submit that the amendments are fully supported by the original specification. For example, the specification describes that expression of the target gene is attenuated by 7.4 fold and 6.2 fold (page 8, lines 23-29), or 6-7 fold (page 37, lines 9-11 and 33-35). In addition, the specification teaches that "[i]n certain preferred embodiments, expression of the target gene is attenuated by at least 5 fold, and more preferably at least 10, 20 or even 50 fold" (page 3, lines 27-28). Given the ample teachings of the specification and the knowledge in the art at the time the application was filed, one skilled in the art would readily practice the claimed invention without undue experimentation.

In view of the arguments and amendments presented above, Applicants submit that all pending claims as amended fully comply with the enablement requirement. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. 112, first paragraph, are respectfully requested.

Claim rejections under 35 U.S.C. § 112, second paragraph

Claims 1, 3-4, 9-10, 12-15, and 26-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Applicants traverse this rejection to the extent that it is maintained in light of the amended claims.

Specifically, the Examiner asserts that the term "stringent" is not defined in the specification or claims. Applicants contend that the term "stringent conditions" is art-recognized. The claims recite the term "stringent" to characterize the hybridization conditions. In the parlance of the molecular biologist, the composite term "stringent (hybridization) conditions" has come to signify those conditions of heat and salt which are standard for the detection of genes in mammals using a hybridization-dependent detection method such as a Southern Hybridization (see, e.g., pp. 9.47-9.57 of Sambrook, Fritsch and Maniatis (1989) Molecular Cloning, 2nd ed., Cold Spring Harbor Press). Thus, to one of skill in the art, the term "stringent" is not ambiguous. Nevertheless, solely to expedite prosecution, Applicants have amended claim 1 to explicitly specify the stringency conditions. Such amendment is fully supported by the specification (e.g., page 17, lines 19-21).

Further, the Examiner asserts that claim 27 lacks proper antecedent basis for "said complementary guide sequences." As described above, claim 27 has been canceled, rendering the rejection moot.

Based on the amendments and arguments presented above, Applicants submit that all claims as amended comply with the requirement of 35 U.S.C. 112, second paragraph. Therefore, reconsideration and withdrawal of rejections under 35 U.S.C. 112, second paragraph, are respectfully requested.

Claim rejections under 35 U.S.C. § 102:

Claims 1, 3-4, 9-10, 12-14, 26-27, and 29 are rejected under 35 U.S.C. 102(e) as allegedly being anticipated by published Li et al. U.S. Patent Filing 2002/0114784 (herein the "Li et al. Published Application"). Applicants respectfully traverse this rejection. The Examiner contends that the teachings of the Li et al. Published Application anticipate the claimed subject matter. The Li et al. Published Application contains a single sentence referring to hairpin constructs. Numbered paragraph 0036 of the published application states

> The dsRNA is formed from one or more strands of polymerized ribonucleotide. When formed from only one strand, it takes the form of a self-complementary hairpin-type

molecule that doubles back on itself to form a duplex. When formed from two strands, the two strands are complementary RNA strands. The dsRNA can include modifications to either the phosphate-sugar backbone or the nucleoside. For example, the phosphodiester linkages of natural RNA may be modified to include at least one of a nitrogen or sulfur heteroatom. Likewise, bases may be modified to block the activity of adenosine deaminase.

The Li et al. patent application was filed 4 January 2002. According to data in the public PAIR database, the Li et al. filing claims priority to, as a continuation, to USSN 09/493,301 filed 28 January 2000 (now abandoned), and claims to two provisional applications, USSN 60/175,440 filed 11 January 2000 and USSN 60/117,635 filed 28 January 1999. Copies of the specifications of the two provisional applications were obtained through the public inspection database at www.epoline.org for Published EP application EP1147204 – which also claims priority to both provisional applications. Copies of both provisional applications will be submitted at the Examiner's request. Neither of the provisional applications include the reference to hairpin constructs found in the Li et al. Published Application. Accordingly, the effective date of the Li et al. reference, for purposes relied on by the Examiner, is 28 January 2000.

Applicants contend that the teachings of Li et al. are not appropriately enabling, as set forth in further detail below. Furthermore, as evidenced by the attached Declaration of Gregory J. Hannon under 37 CFR 1.131 (the "Hannon Declaration") and the exhibits attached thereto, the inventors had possession of the subject matter disclosed in Li et al. and relating to hairpins before the January 28, 2000 effective filing date of the Li et al Patent Application.

Li et al. Published Application is not enabling

In considering the effect of the Li et al. Published Application, it is important to also understand that it was necessary to know the mechanism by which RNA interference ("RNAi") works in order to appreciate that hairpin RNAs could be used to induce gene silencing in mammalian cells. That is, in order for those skilled in the art to reasonably believe that a hairpin RNA could induce gene silencing, they first needed to understand the cellular mechanism by which double stranded RNA could induce sequence-specific gene silencing. As detailed in the Hannon Declaration, at the time of the filing of the Li et al. Published Application, that mechanism was not known to the public nor described in the Li et al. Published Application. The Li et al. Published Application is entirely silent on the mechanism of RNAi.

At the time the Li et al. Published Application was filed in January 2000, procedures based on double stranded RNA-triggered silencing were fairly well-established tools for

functional genomics of lower organisms (plants, invertebrates and fungi). The ability of a few molecules of double stranded RNA to eliminate a much larger pool of endogenous mRNA had suggested a catalytic or amplification component to the interference mechanism. For instance, some of the plant literature favored an RNA-based copying system that was proposed to produce copious amounts of antisense RNA (while perhaps also producing additional sense and dsRNA). See Jorgensen et al. (1998) Science 279: 1486; Waterhouse et al. (1998) Proc. Natl. Acad. Sci. 95:13959 and Wassenegger et al. (1998) Plant Mol. Biol. 37:349. If that had indeed been the mechanism, it would not be apparent how hairpin RNA could substitute for double stranded RNA.

At the time the Li et al. Published Application was filed, one could certainly have hoped that RNA-triggered silencing would exist in vertebrates. However, the simple protocols used for invertebrate and plant systems were known not to be effective in mammalian cells. At that time, it was recognized in the art that there were several impediments to the use of RNAi in normal mammalian cells. Most mammalian cells harbor a potent antiviral response that is triggered by the presence of dsRNA viral replication intermediates. Reviewed Williams (1997). Biochem. Soc. Trans. 25, 509-513 and Gil (2000). Apoptosis 5, 107-114. In somatic cells, dsRNA activates a variety of responses. Predominant among these is PKR, a kinase that is activated by dimerization in the presence of dsRNA (Clarke et al. (1995) RNA 1, 7-20). PKR, in turn, phosphorylates EIF2α, causing a nonspecific translational shutdown. dsRNA also activates 2'-5' oligoadenylate polymerase, the product of which is an essential cofactor for a nonspecific ribonuclease, RNase L. Reviewed in Baglioni et al. (1983). Interferon 5, 23-42. The ultimate outcome of this set of responses is cell death via apoptosis.

The recapitulation of the essential features of RNAi was a prerequisite for a biochemical analysis of the phenomenon. In the absence of the biochemical and genetic approaches carried out by the inventors in several experimental systems and described in the instant application, those skilled in the art would have had no reasonable expectation that, based on the teachings of the Li et al. Published Application, hairpin RNA would have any effect as a gene silencing agent in mammalian cells. Understanding the mechanisms underlying RNAi in both invertebrates and vertebrates would have been required to recognize the utility of hairpin RNA for inducing gene silencing by an RNAi pathway. That understanding come from the work of the present inventors, who identified the existence of conserved machinery for double stranded RNA-induced gene silencing from drospohila to mammals. They also defined the RNAi process as proceeding via a two-step mechanism. In the first step, double stranded RNA is recognized by an RNase III family nuclease called Dicer, which cleaves the dsRNA into about 21-23-nt siRNAs (now called "small interfering RNA" or "siRNA"in the scientific literature). These siRNAs are

incorporated into a multicomponent nuclease complex, RISC, which identifies substrates through their homology to siRNAs and targets these cognate mRNAs for destruction.

Antedating of Li et al. Published Application

The Li et al. Published Application is not prior art to the subject matter of the pending claims. The attached Declaration of Gregory J. Hannon under 37 CFR 1.131 establishes that the inventors had possession of the subject matter disclosed in Li et al. Published Application prior to the effective date of that reference. Applicants' declaration antedates the Li et al. reference and removes Li et al. from consideration as prior art. Therefore, Applicants' declaration under 37 CFR 1.131 obviates the rejection under 35 U.S.C. 102(e). Reconsideration and withdrawal of this rejection are respectfully requested.

Double patenting

Claims 1, 3-4, 9-10, 12-15, and 26-29 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-2, 8-9, 13-18, and 20 of U.S. Patent Application No. 10/350,798. Applicants enclose herewith a terminal disclaimer which is believed to obviate the objection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

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